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Certificate

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of Correction

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:

Richard POULIN et al.

Patent N°

6,949,679 B

Filed:

Ferbuary 9, 2000

Title:

POLYAMINE TRANSPORT INHIBITORS

REQUEST FOR A CERTIFICATE OF CORRECTION

U.S. Patent and Trademark Office Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450

Sir:

Enclosed herewith is a copy of the official Patent for which a certificate of correction is required:

The name of the third inventor "René Charest-Gaudrealt" should read -- René Charest-Gaudreault --.

Please correct accordingly and provide us with a Certificate of Correction.

Respectfully submitted,

Richard POULIN et al.

By:

October 13, 2005

Date

Patrice Préville (Reg. No. 56,873)

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Enc. Copy of first page of Patent

(12) United States Patent Poulin et al.

(10) Patent No.: US 6,949,679 B1 (45) Date of Patent: Sep. 27, 2005

(54) POLYAMINE TRANSPORT INHIBITORS

(75) Inventors: Richard Poulin, Sainte-Poy (CA); Marle Audette, Cap-Rouge (CA); Rene

Charest-Gaudrealt, St. Nicolas (CA)

(73) Assignee: Universite Laval, Québec (CA)

Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35

U.S.C. 154(b) by 0 days.

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U.S. Cl. 564/s12

(58)Field of Search 564/512, 154;

514/625; 424/78.27, 78.37, 78.35

(56)References Cited

U.S. PATENT DOCUMENTS

8/1965	Dickson et al 530/231
* 8/1965	Spivack 564/512
* 12/1986	Tomalia et al 528/391
2/1991	Johnson et al.
10/1995	Aziz ct al 424/78.08
* 7/2000	Poulin et al 424/18 27
• 1/2004	Woods et al 156/314
	* 8/1965 * 12/1986 2/1991 10/1995 * 7/2000

FOREIGN PATENT DOCUMENTS

WO	WO93/04373	3/1993
WO	WO 93/12777	7/1993
WO	WO 98/17623	4/1998

OTHER PUBLICATIONS

Hubert et al. Journal of Biological Chemistry, vol. 271, No. 44, pp 27556-27563, 1996.*

Patricia Hubsch-Weber et al., Synthesis and Characterization of a New Series of [12] aneN, Type Macrocycles. Structures of two Protonated Metal-Free Ligands. Tetrahedron Letters, Vo. 38, No. 11, pp. 1911-1914, 1997.

Huber ct al., (N-ethyl-spermine-5-carboxamide) Is a High Affinity, Membrane-impermeant Antagonist of the Mammalian Polyamine Transport System. The Journal of Biological Chemistry, vol. 271, No. 44, 1996, pp. 27556-27563.

Egon Buhleier et al., "Cascade"-and "Nonskid-Chainlike" Synthesis of Molecular Cavity Topologies. Georg Thieme Publishers, pp. 155-158, 1978.

Ask et al., "Antileukemic effects of non-metabolizable derivatives of spermidine and spermine," Cancer Lett., 66:33-38, 1993.

Ask et al., "Increased survival of L1210 loukemic mice by prevention of the utilization of extracellular polyamines. Studies using a polyamine-uptake mutant, antibiotics and a polamine-deficient diet," Cancer Lett., 66:29-34, 1992.

Aziz et al., "A novel polymeric spermins conjugate inhibits polyamine transport in pulmonary artery amouth muscles cells," J. Pharmacol. Exper. Ther., 274:181-186, 1992.

Aziz et al., "The potential of a novel polyamine transport inhibitor in cancer chemotherapy," Pharmacol. Exper. Ther., 278:185-192, 1996.

Bergeron et al., "Development of a hyposine reagent for peptide synthesis," Org. Chem., 62:3285-3290, 1997.

Chaney et al., "Tumor selective enhancement of radioactivity uptake in mice treated with β -difluoromethylomithine prior to administration of ¹⁴ C-putrescine, Life Sci., 32:1237-1241, 1983.

Chang et al., "Modulation of polyamine biosynthesis and transport by oncogene transfection," Biochem. Biophys. Res. Comm., 157:264-270, 1988.

Cohen et al., Targeting of cytotoxic agents by polyamines:synthesis of a chlorambucil-spermidine conjugate," J. Chem. Soc. Chem. Commun., pp. 298-300, 1992.

Duranton et al., "Suppression of preneoplastic changes in the intestine of rats fed low levels of polyamines," Cancer Res., 57:573-575, 1997.

Felschow et al., "Photoattinity labeling of a cell surface polyamine binding protein," 270:28705-28711, 1995.

Prebort and Adachi, "Copper/quinone-containing amine oxidases, an exciting class of ubiquitous enzymes," J. Ferment. Bioeng., 80:625-632, 1995.

Hayashi et al., Ornithine decarboxylase antizyme—A novel type of regulatory protein, Trends Biochem. Sci., 21:27-30,

He et al., "Antizyme delays the restoration by spermine of growth of polyamine-deficient cells through its negative regulation of polyamine transport," Biochem. Biophys. Res Commun., 203:608-614, 1994.

(Continued)

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(57)ABSTRACT

The present invention describes the design, synthesis and therapeutic use of a variety of novel inhibitors of polyamine transport. The main feature of this class of transport inhibitors is to incorporate a linker or side chain that prevents the uptake of polyamines and helps to conjugate polyamine analogs to form dimers with high inhibitory potency against polyamine uptake. These new compounds incorporate features that are designed to maximize their chemical and metabolic stability and their ability to bind to the polyamine transporter, and to minimize their toxicity by preventing their absorption by the cells. The purpose of such inhibitors is to prevent the uptake or salvaging of circulating polyamines by rapidly proliferating cells such as tumor cells, in order to potentiate the effect of therapeutic inhibitors of polyamine biosynthesis such as alphadifluoromethylomithene.

4 Claims, 35 Drawing Sheets

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